Fast-Tracking Biodefense Vaccines and Therapeutics : An Urgent Challenge We Must Meet

Introduction to CBER Workshop on Development of Counterterrorism Products

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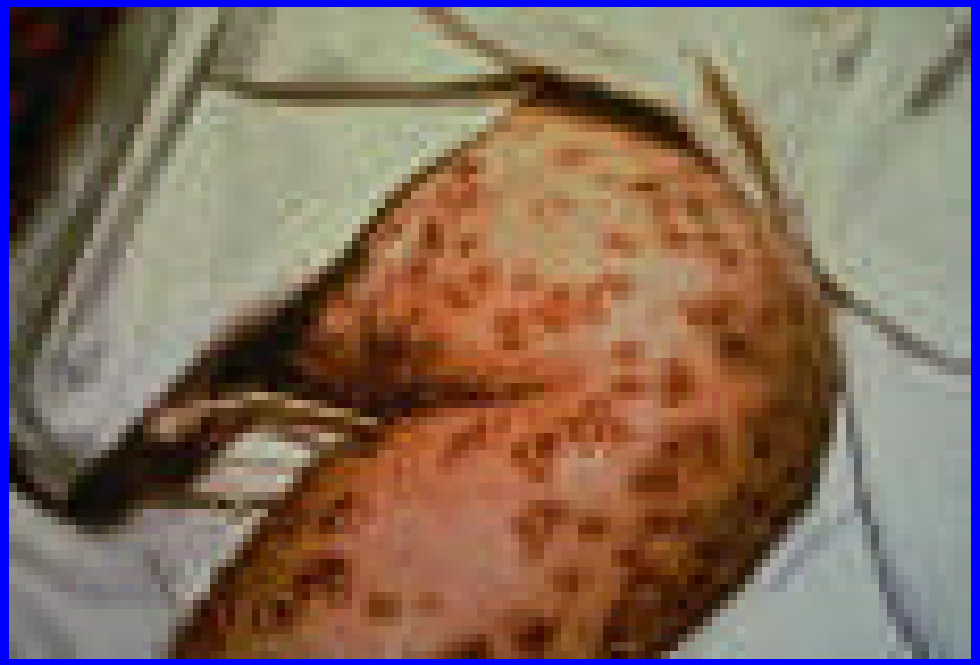
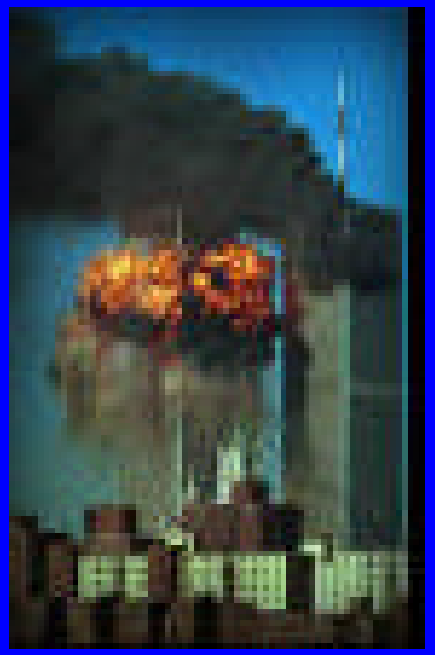




CT: CBER Roles and Products

- **Roles:**
  - **Facilitate Product Development**
  - **Evaluate safety and effectiveness data**
  - **Facilitate Product Availability**
  - **Help assure product integrity**
  - **Related research and regulatory activity**
- **Relevant Products**
  - **Vaccines, Ig, Blood and blood products, gene, cell and tissue therapies**
    - **133 active IND/IDE/MF/ 561 amendments**
    - **93 CT research projects for unmet needs**

Workshop Goals

- **Help provide overview of all phases of CT product development process**
- **Share experience, lessons learned and help avoid common pitfalls, road bumps**
- **Stimulate interest, initiate dialogue, address FAQs**

Assist in the more efficient development of new & innovative products for biologic, chemical and radiologic defense

Approaches to Speed Product Availability or Licensure

- Early and frequent consultation between sponsor, end user (if different) and FDA
- Availability for emergency use under IND
- Fast track and accelerated approval processes
- Priority review
- Approval under “Animal Rule”
- Careful attention to risk:benefit and risk management issues
- Incentives

PD Path, Milestones and Usual Recommended Meetings

Pre-IND Meeting:

- -Manufacturing
- -Lot Release
- -Animal safety & immunogenicity
- -Phase 1 protocol

End-of-Phase 2 Meeting:

- -Phase 3 protocol(s)
- -Phase 1 & Phase 2 data
- -Animal efficacy protocols & data (if "animal rule" used)
- -Update on manufacturing & lot release

Pre-BLA Meeting:

- -Clinical data summary: Safety & Efficacy data
- -Manufacturing, etc.
- -Outline of BLA

Phase 1 → **Phase 2** → **Phase 3** → **License Application**

Risk Management

IND = Investigational New Drug Application
BLA = Biologics License Application

Early and Frequent Consultation

- Improves communication process
- Improves quality of laboratory and clinical studies
- Reduces misunderstandings and likelihood of unwelcome “surprises”, multiple review cycles
- Improves efficiency of product development
- Very resource intensive for FDA
- Product teams at CBER being used for this purpose for priority BT product development and review (e.g. smallpox, anthrax vaccines)

Availability Under IND

- Can allow rapid access to an unlicensed product if there is an emergency need
- Simplification, flexibility for CT/BT issues
- Work towards licensure, wherever feasible
- Rapid turnaround/active assistance from FDA; “streamlining”, multiple media etc.
  - recent examples in smallpox, anthrax, botulism

Pros and Cons of Availability Under IND

- **Pros**
  - **Clarity that a treatment is not a standard licensed therapy equivalent to routine prescription drugs**
- **Cons**
  - **Potentially Cumbersome**
    - **Especially in emergency e.g. witnessed, written consent**
  - **Connotation of “Experimentation”**
  - **Addressed by Bioshield**

Emergency Use Authorization Proposal in *Bioshield*

- **EUA – the nuts and bolts**
  - **An emergency must be declared by the Secretary of Homeland Security (national) or Secretary of Defense (military) or Secretary of HHS (public health)**
  - **The Secretary of HHS must issue the EUA (likely delegated to FDA)**
  - **The product must be for an agent that can cause a serious or life-threatening disease or condition; there is no adequate, approved, and sufficiently available product**
  - **The product's known and potential benefits must outweigh its known and potential risks (a challenge to define standards)**
  - **The product's use and/or distribution may be limited**
  - **The authorization will be time limited and can be terminated**

Emergency Use Authorization II.

- EUA – the nuts and bolts (continued)
  - Certain information to the user/consumer is required, if feasible
    - product authorized for specific emergency use
    - the significant risks and benefits of the product
    - alternatives
    - option to accept or refuse administration
  - Appropriate information about the emergency use may be collected, if feasible

Priority Review

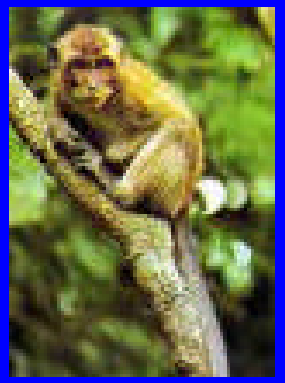
- Product is a significant advance (drugs)
- For serious or life threatening illness (biologics)
- 6 month complete review of license application
- Recent example: pneumococcal conjugate vaccine
- Most CT products expected to qualify

Fast Track, Accel. Approval

- Serious/life-threatening: meaningful therapeutic benefit over existing Rx.
- Allows for rolling submission
- Accel. approval:
  - Utilize surrogate endpoints likely to predict clinical benefit (314.510, 601.40)
    - E.g. CD4 cells for HIV, clinical markers (BP)
  - Post-licensure studies required (usually ongoing) to demonstrate effects on disease outcomes
  - Restrictions on use or distribution possible
  - Potential problems obtaining controlled data
- Withdrawal if agreements violated/not S&E
- Can approve through regular mechanisms with validated surrogate (e.g. protective Ab)

Animal Rule

- **Drugs & biologicals that reduce or prevent serious or life threatening conditions caused by exposure to lethal or permanently disabling toxic chemical, biological, radiological, or nuclear substances**
- **Human efficacy trials *not feasible or ethical***
- **Use of animal efficacy data scientifically appropriate**



Animal Rule II.

- **Still need human clinical data:**
  - **PK/immunogenicity data**
  - **Safety in population(s) representative of use**
    - **Civilian use often includes pregnancy, children**
- **Approval subject to post-marketing studies, any needed restrictions on use**
- *Potential limitations:*
  - **Where there is no valid animal model of disease**
  - **How to predictably bridge animal data to humans**
  - **Confidence may be an issue, even in valid models**

Potential Incentive Approaches for Product Development

- Existing:
  - Expedited regulatory pathways
  - Orphan status; < 200k patients; 7 yr exclusivity
- Other possibilities
  - Push: direct financial rewards, tax credits, exclusivity, partnerships, R&D assistance (e.g. basic, proof of principle, pilot lot production, clinical)
  - Pull: known markets, longer term contracts, prices proportional to public health benefit, dual uses (non-BT)
  - Addressing liability issues
- *Bioshield*
  - New indefinite spending authority for critical countermeasures
    - ~ $ 1 b FY04; SP, anthrax, bot; $ ~6 b over coming years

FDA/CBER BT Research: Focus on Critical Pathways to Development

- ***Generally target unmet needs with regulatory implications to facilitate the development of products***
  - **Better determine potency**
  - **Immunogenicity/protection, disease models, correlates**
  - **Assuring safety (e.g. cell lines, adventitious agents)**
  - **Make regulation more scientific, less "defensive"**
  - **Benefit multiple companies across industry**
- **Maintain staff "cutting edge" expertise needed for dealing with evolving biotechnologies**
- **Scientific expertise and confidence foster objectivity**
  - **Reduces risks of reflexive over- or under-protectiveness**

CBER Research in BT: II.

- **Examples of current studies on threat pathogens**
  - Smallpox**: assay for immune response and potency, risk assessment on vaccine strategies and blood safety**
  - Anthrax**: Improved immunologic assays**
  - VIG**: Identification of protective isotypes, assays of commercial IGIV for activity, animal efficacy**
  - Tularemia**: correlates of immunity**
  - Botulinum toxin**: cellular trafficking of toxin, mechanisms of neutralization**
  - General**: stimulation of innate immunity/adjuvants**
- ***As you develop products, we welcome your input as to unmet scientific needs***

Risk/Benefit for CT Products

- **Risk:benefit differs and is assessed by FDA for each product & potential use**
  - ***Treatment*: For CT related products which have impact on otherwise untreatable serious illness, reasonable to tolerate significant risk & some uncertainty (but desirable to reduce)**
  - ***Prophylaxis*: If given to well individuals before event or, post-event, to individuals who may not be at risk, balance shifts**
- **For lethal disease, *lack of efficacy is a safety issue***
  - **Ill-placed confidence**
  - **Something is not always better than nothing**
  - **Acceptance of an ineffective therapy may inhibit development or use of a more effective one**
- **All such products:**
  - **Need for honest and effective/efficient (*vs. legalistic*) risk communication process, *which may be quite challenging in unanticipated emergency settings***

Regulation and BT Products: What is the value added?

- As for other medical products (but perhaps even more important): need for consistent and objective protection of the public's safety *and need for trust*
- BT a moving target, no predictable epidemiology;
  - witness post-anthrax experience, extension of military products to broader or older populations
- The public expects safe (and effective) and products, especially vaccines given to well individuals, and looks to FDA for protection and reassurance.
- Preserving confidence in medical products, and in public health leadership, is critical.
  - When things go "wrong" (or even if someone just thinks they did); few will remember the crisis


GO ON IN, IT'S SAFE!


SPECIAL INVESTIGATION
LIFE
The Tiny Victims of Desert Storm
Has Our Country ABANDONED THEM?

What FDA Cannot Do

- Provide monetary or tax incentives
- Assure that anyone makes a product
- Advanced product development (conflict of interest)
- Provide indemnification or compensation
- Guarantee absolute safety
- Guarantee efficacy based on non-human data or based on non-BT experience

What FDA Can Do

- Work with partners to identify unmet public health needs and coordinate responses
- Encourage sponsors to make needed products and facilitate their development through regulatory process: why we are here today!!!!
- Perform research that facilitates product development, safety and improves regulation
- Provide intensive & early interactions and regulatory priority where appropriate
- Increase confidence in efficacy of products
- Reduce likelihood of serious adverse events
- Partner with other agencies, health systems to improve monitoring of product use

Recent and Ongoing CBER Actions

- Meetings to encourage developing new products
- Early interactions w/ sponsors
- Collaboration and rapid turnaround on INDs
- Proactive trips to examine facilities
- Participation in multiple interagency and interdepartmental teams.
- Expedited approval of key product(s) apps.

Resource intensive but critical

"Can't you ever relax!"

Thanks!

www.fda.gov/cber

- **Email**
  - **Manufacturers: matt@cber.fda.gov**
  - **Consumers, health care: OCTMA@cber.fda.gov**
- ***Questions/comments now or later?***
- ***As new CBER Director, I ask that you take advantage of your opportunity to help us move forward.***
  jgoodman@cber.fda.gov
- ***We are very willing to work closely with investigators and sponsors of important BT products.***
- ***We look forward to this meeting and welcome your input.***
- ***Tremendous interest and we plan to modify as needed and repeat if successful.***